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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,645	10/31/2000	Rainer Haas	100564-00035	6963

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,645	HAAS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,57-63 and 65-103* is/are pending in the application.

4a) Of the above claim(s) *59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53, 57, 58, 60-63, 65-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed May 6, 2004. Claims 53, 57-63 and 65-103 are pending. Claim 59 is withdrawn from consideration as being drawn to a nonelected invention. Applicants arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. It is noted that this application has been examined only to the extent that the claims are limited to the subject matter elected in the response of Paper No. 9. The elected subject matter is a method for detecting macrolide antibiotic resistance in Helicobacter, in particular, using probes comprising SEQ ID NO: 1. The non-elected subject matter which has not been examined includes claim 59, SEQ ID NO: 2-4 in claims 57-59, 78, 92 and 93, non-elected regions in claim 60 and non-elected microorganisms in claim 62.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53, 57-58 and 60-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting clarithromycin resistance in H. pylori wherein the methods comprise detecting the presence of a A to G or A to C mutation at position 2058 of the 23S rRNA of H. pylori as indicative of resistance of H. pylori to clarithromycin, does not reasonably provide enablement for

methods of detecting antibiotic resistance in any microorganism by detecting any mutation in any peptidyltransferase center of 23S rRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are very broadly drawn to methods for detecting macrolide antibiotic resistance in a microorganism wherein the methods comprise hybridizing a nucleic acid sample with a probe that is specific for the peptidyltransferase center of 23S rRNA in any microorganism which is associated with resistance to any antibiotic. The specification teaches (see, for example, page 6) six mutations in the 23S rRNA gene which result in resistance to the antibiotics chloramphenicol, clarithromycin, clinidamycin, erythromycin, linomycin and/or streptomycin in E.coli, P. acnes, M. pneumoniae, M. intracellular and/or H. pylori. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is

unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional mutations in the 23S rRNA gene will result in resistance to antibiotics. The claims include an incredibly large genus of mutations which have not been adequately taught in the specification. The specification does not provide sufficient guidance as to how to identify additional mutations which confer resistance to antibiotics and which are specific for a microorganism. To identify additional mutations associated with antibiotic resistance in microorganisms would require extensive analysis of a large genus of 23S rRNA sequences from a representative number of microorganisms for the presence of a mutation associated with resistance to any one of a large number of possible antibiotics and then developing probes which are specific for that microorganism. Such experimentation is considered to be undue. As set forth on page 6 of the specification, the specified 23S rRNA mutations confer resistance to different antibiotics in different microorganisms. For example, the 2058 mutation in the 23S rRNA confers resistance to clarithromycin in H. pylori, but confers resistance to erythromycin in M. pneumoniae. Accordingly, there is no predictable means for determining which mutations confer resistance to which antibiotics in a given microorganism. While the specification exemplifies methods which analyze the 23S rRNA for the presence of mutations at positions 2032, 2057, 2058, 2059, 2503 or 2611 in 5 microorganisms, only the mutation at position 2058 has been shown to confer antibiotic resistance H. pylori. The 2058 mutation has not been shown to confer resistance to any additional antibiotics in H. pylori and the 2058 mutation has not been shown to confer antibiotic resistance to any additional species of Helicobacter. The

specification has not established that the stated mutations confer resistance to all antibiotics or that these mutations confer antibiotic resistance in all microorganisms. The ability to establish a correlation between the presence of a mutation and the occurrence of antibiotic resistance is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. The claims require the use of probes that detect resistance to macrolide antibiotics. Such probes must hybridize to specific mutations in the 23S rRNA peptidyltransferase center wherein said mutations confer resistance to one of a multitude of macrolide antibiotics; 2) must specifically detect the microorganism; and 3) must be able to distinguish between a perfectly matched versus a mismatched sequence under in situ hybridization conditions. The specification has not adequately taught or provided sufficient guidance to obtain a representative number of such probes. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the response filed May 6, 2004, Applicants traversed the above rejection by stating that the "problem underlying the present invention is not the identification of new point mutations in the peptidyl transfer center responsible for antibiotic resistance. Instead, the present invention exploits known point mutations responsible for antibiotic resistance." However, the present claims are not limited to methods for detecting these known mutations. Rather, the present claims allow for the detection of any mutation in

the peptidyl transferase region of any microorganism wherein the mutation is associated with any type of macrolide antibiotic resistance.

It is argued that the specification teaches conserved positions in the peptidyl transferase region and that the skilled artisan would take these conserved positions into consideration "when looking for point mutations responsible for antibiotic resistance." However, again, the claims are not limited to methods which detect specific, known point mutations in the peptidyl transferase region. Thereby, the skilled artisan is left to analyze the conserved and nonconserved sequences of the peptidyl transferase region in Helicobacter or in any microorganism in order to identify additional mutations associated with macrolide antibiotic resistance. In view of the unpredictability in the art, such random experimentation is considered to be undue. As set forth in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the novel aspects of the invention include the specific mutations in the peptidyl transferase region which are associated with antibiotic resistance. However, the claims are not limited to specific mutations taught in the prior art to be associated with resistance to particular macrolide antibiotics in particular organisms. Rather, the claims and specification require that the skilled artisan search for additional mutations and analyze known mutations in order to try to determine which ones, if any, are associated with a particular type of antibiotic resistance in a particular microorganism. For the mutations which are known, there is no universal association between the mutations and all types of antibiotic resistance in

all organisms. Rather, only particular point mutations are associated with resistance to specific antibiotics and this association varies between microorganisms. Thereby, identifying additional mutations and establishing an association between a mutation and antibiotic resistance in particular microorganisms can only be accomplished through trial-by-error experimentation.

Applicants further point to the teachings of Wang as teaching that the peptidyl transferase center consists of a limited number of nucleotides. It is asserted that since macrolide antibiotics have a common mode of action , "a person skilled in the art need not assign specific point mutations in the peptidyl transferase center to specific macrolide antibiotics." It is stated that the region covering 2057, 2058 and 2059 is strongly conserved among microorganisms and therefor point mutations in other organisms leading to antibiotic resistance would occur at identical positions. These arguments have been fully considered but are not persuasive. Again, the majority of the claims are not limited to the mutations at 2057, 2058 and 2059. Further, the teachings in the specification indicate that while a mutation may be present at an identical position, this mutation is not necessarily associated with antibiotic resistance in other microorganisms. That is, the location of the mutation alone does not provide a predictable means for determining whether a microorganism will be resistance to a macrolide antibiotic. The unpredictability associated with detecting additional mutations is also emphasized by Applicants own arguments. In the response of May 6, 2004, Applicants state that "Prior to the present invention, no other point mutation was detected in this region which was responsible for antibiotic resistance. A person skilled

in the art would therefore, regard the other positions of the peptidyl transferase center as **not being relevant regarding antibiotic resistance** and the selection of a point mutation as a matter of routine experimentation." The statement that other positions in the peptidyl transferase region should be considered irrelevant regarding antibiotic resistance clearly emphasizes the unpredictability in identifying additional positions that are associated with antibiotic resistance. Again, the claims are not limited to the specific mutations taught in the prior art as being associated with macrolide antibiotic resistance in particular microorganisms. If it is Applicants belief that other positions in the peptidyl transferase region are not associated with antibiotic resistance, then the claims should be amended to exclude this large genus of inoperable embodiments and the claims should be limited to those embodiments which have been shown to be operable, i.e., to the specific mutations known to be associated with particular antibiotics in particular microorganisms.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53, 57-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53, and 57-85 are indefinite over the recitations of "microorganisms which are treated using macrolide antibiotics" because it is not clear as to how this recitation is intended to limit the claims. It is unclear as to whether this is considered to be a property of the microorganisms (e.g., that an individual infected with the microorganism

can be treated with a macrolide antibiotic; that the microorganism is sensitive to the macrolide antibiotic) or if the claim is intended to include a step of treating the microorganism with the antibiotic. Furthermore, it is unclear as to what is intended to be meant by the phrase "wherein said microorganisms are usually sensitive to macrolide antibiotics." The claims do not set forth the conditions or circumstances for treatment with antibiotics and it is unclear as to what is meant by the fact that the microorganisms are **usually** sensitive to the antibiotic since the claims do not clarify the conditions which under which the microorganisms are sensitive or insensitive to the antibiotic.

RESPONSE TO ARGUMENTS:

In the response filed May 6, 2004, Applicants state that the above rejections have been overcome by the amendments to the claims. However, the amendments do not obviate the above rejections. It remains unclear as to how the recitation of "microorganisms which are treated using macrolide antibiotics" is intended to limit the claims. Further, it is unclear as to what is meant by microorganisms which are "usually sensitive to macrolide antibiotics." When are the microorganisms sensitive and when are they not sensitive to macrolide antibiotics? The conditions for ascertaining what is intended to be encompassed by "usually" are not set forth in the claims and are not defined in the specification.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53, 57-58, 60-85, 92, 93, and 101-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Microbiological Reviews (March 1995) 59: 143-169) and Amann (Journal of Bacteriology (1990): 172: 762-770).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference also teaches that an A to a G mutation at position 2059 confers resistance to clarithromycin in H. pylori. The reference teaches that the mutations can be detected by sequencing the nucleic acids of H. pylori and by restriction enzyme analysis. However, the reference does not teach detecting the mutations by performing in situ hybridization.

Amann (1995) teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe specific for a target rRNA sequence and subjected to hybridization (see, for example, pages 147-148 and 152-153). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome. Amann (for example, pages 156-157) also teaches using a mixture of probes so that multiple microorganisms can be detected simultaneously. Amann (page 158-166) addresses several criteria which may effect in situ hybridization efficiency and provides guidance as to how to improve the specificity and sensitivity of in situ hybridization. In particular, Amann acknowledges that some regions of the rRNA are less accessible for hybridization to probes due to the presence of secondary structures in the rRNA (see pages 159-160). Amann outlines the steps for evaluating the ability of a probe to effectively hybridize to the rRNA in situ and teaches how to optimize probes with respect to selecting an appropriately accessible target sequence, selecting optimal probes and hybridization conditions based on the probe's temperatures of dissociation. AT page 160, Amann states that "There is some indication (although from negative results) that certain regions might be inaccessible in certain phylogenetic groups. Sometimes, shifting the target site by just a few nucleotides has a major influence on the probe sensitivity." Amann (page 160) also teaches effective methods for labeling probes in order to enhance the sensitivity of in situ hybridization. Accordingly, Amann provides ample guidance as to how to effectively select and use a 23S rRNA probe for in situ hybridization and detection of a specific microorganism.

Additionally, Amann (1990) teaches in situ hybridization methods for detecting specific microorganisms. Amann teaches that in situ hybridization methods can be used to discriminate complementary from single-mismatched hybrids (see page 765).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Versalovic so as to have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and rapid means for detecting clarithromycin resistance in H. pylori.

Further, Versalovic does not teach analyzing the sample without culturing. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. Amann (1995) teaches facilitating the detection process by concentrating the cells (page 158) and teaches methods for improving the sensitivity of detection by using multiple labels and more sensitive labels (page 160) and by using improved instrumentation for detection of labeled probes (page 162). One of ordinary skill in the art would have been motivated to have omitted the culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claims 66 and 67, Versalovic teaches obtaining the H. pylori from patient samples and transferring the sample to a "presumptive medium" containing an indicator. With respect to claims 89, 90, 96 and 97, Versalovic teaches growing H. pylori

in brain heart infusion agar containing fresh horse blood. It is a property of this media that it contains the reducing agent cysteine and a nitrogen source.

With respect to claims 68 and 69, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to probes, Versalovic teaches a 19 bp region of 23S rRNA containing the 2058 mutation and Amann (1990) teaches the use of oligonucleotide probes of 15 to 25 nucleotides (page 763). Accordingly, it would have been obvious to one of ordinary skill in the art to have generated probes complementary to the regions set forth by Versalovic wherein said probes are 15-25 nucleotides in length in order to have provided probes useful for detecting the 2058 mutation. Probes complementary to the region set forth by Versalovic comprise at least 10 nucleotides of SEQ ID NO: 1. The sequence complementary to the region disclosed by Versalovic differs from present SEQ ID NO: 1 only in that it is missing a 3' T nucleotide. However, the sequence of the 23S rRNA of H. pylori was well known in the art at the time the invention was made. Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of up to 25 nucleotides complementary to the region. Amann (1995 and 1990) also teaches using multiple probes simultaneously. Accordingly, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type

probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori.

Further, Amann (1995 and 1990) exemplifies the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have included a genus or species specific probe in order to have confirmed the identity of the organism. It is noted that Versalovic teaches examining H. pylori microscopically (page 477) and quantitatively detecting clarithromycin resistance (page 478).

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed the above rejection. Applicants state that Amann teaches that single-mismatch discrimination must be empirically established and that the ability to discriminate complementary and mismatch hybrids varied markedly between different probes and target sequences. Applicants assert that the combined references do not provide a reasonable expectation for success. However, there are no teachings in Applicant's specification which would allow one of skill in the art to achieve results that are an improvement over those achieved by Amann. Applicants do not teach any particular conditions or probes which will allow one to achieve discrimination between complementary and mismatch hybrids without any experimentation. What are the conditions, probes and method steps employed by Applicants that would allow one to predictably distinguish between any mismatch and complementary nucleic acid hybrid using any probe to a peptidyltransferase region from any organism? Applicants response should clarify where the specification teaches conditions, probes and method steps that will allow for an improvement in discrimination

over that achieved by Amann. Further, Applicants should point out where these limitations are set forth in the claims. Additionally, it is maintained that the combined references do allow for a reasonable expectation of success because Amann (1995 and 1990) provides the guidance for selecting and developing probes that hybridize to rRNA and which can be used to discriminate between perfectly matched and mismatches hybrids.

Applicants assert that the teachings in the cited prior art do not provide a reasonable expectation of success. The specification acknowledges, as does Amann (1995), testing is required to identify probes that can be used for in situ hybridization. The specification does not assert that it is unexpected that one could use a probe to detect mismatches in the rRNA and does not provide any guidance beyond the teachings of Amann for improving the method of in situ hybridization so as to allow for a more predictable means of detecting mismatches in rRNA. The "unexpected results" proposed by Applicants are not commensurate in scope with the teachings of the specification. The specification has taught only 4 probes that can be used to screen for Helicobacter clarithomycin resistance using in situ hybridization methods by detecting a single-nucleotide mutation in the 23S rRNA of Helicobacter, i.e., the probe ClaR1 which consists of SEQ ID NO: 1 and which detects the A2058G mutation, probe ClaR2 which consists of SEQ ID NO: 2 and which detects the A2059G mutation, probe ClaR3 which consists of SEQ ID NO: 3 and which detects the A2058C mutation, and the probe ClaWT which consists of SEQ ID NO: 4 and which detects wildtype Helicobacter. In view of the fact that Amann provides the guidance for performing in situ hybridization for

the detection of point mutations, the ordinary artisan would have had a reasonable expectation of success of generating additional probes, commensurate in scope with the presently claimed probes, which could be effectively used for in situ hybridization to detect point mutations in H. pylori.

Applicants state that the claims have been amended to recite that the hybridization step is performed without prior culturing of the microorganisms. It is stated that Amann (1990) teaches analysis of microorganisms at mid-log phase when the cells are growing the fastest and that even under optimal conditions there is only weak discrimination between Fibrobacter strains. Applicants also state that "Amann (1990) could be interpreted as teaching that it is possible to perform single-mismatch discrimination by in-situ hybridization under optimal conditions. However, Amann indicates that it is necessary to employ cells growing in the mid-log phase which thus have an optimal rRNA content." However, while the present claims exclude culturing of cells prior to hybridization, the claims do not exclude the isolation and in situ hybridization analysis of metabolically active cells. In view of Applicants arguments, the method of Amann would be considered to be fully enabled when the ordinary artisan utilized samples of metabolically active cells. Secondly, Amann does not teach that it is a requirement to grow cells to mid-log phase prior to in situ hybridization. This is a not an accurate characterization of the teachings of Amann. In fact, Amann (1990; page 765, column 1) teaches that hybridization with a combination of two probes approximately doubled the signal intensity. Amann (1990; page 765, column 1) concludes that "multiple probes can be used to alleviate problems of low rRNA content

or reduced target availability in the detection of specific microorganisms." The present invention relies on the same solution. In particular, the specification (page 32) states that "It is particularly important to use both probes simultaneously for detecting H. pylori in situ, in order to detect H. pylori cells which are metabolically less active. As a rule, bacteria whose metabolism is reduced have a lower content of ribosomes or rRNA, resulting in the detection method losing sensitivity, particularly when only one probe is used and this probe is provided with fluorescein, which is a dye which only emits comparatively weakly." Amann (1995, page 160) also teaches that the results of in situ hybridization methods can be improved by using more sensitive labels and by using multiple labels.

Applicants comment that "microorganisms grow rather slowly in most environmental conditions" is not relevant to the present claims since the present claims do not require the analysis of environmental samples, but rather allow for the analysis of any type of biological sample, including clinical samples as taught by Versalovic and Amann (1990).

6. Claims 86-90 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann (1995) and Amann (1990) in view of the Stratagene catalog.

The teachings of Versalovic and Amann (1995 and 1990) 7. are presented above. The combined references teach a method which requires the use of a 23S rRNA probe specific for the 2058 mutation of H. pylori, a presumptive medium, and an

indicator substance for detecting antibiotic resistance. Versalovic does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Versalovic in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect antibiotic resistant strains of H. pylori.

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed the above rejection by stating that Versalovic, Amann (1990) and Amann (1995) do not teach a method of single-mismatch discrimination by hybridization without prior culturing of microorganisms. Applicants state that the Stratagene catalog does not cure this deficiency. This argument is not persuasive because the claims are not drawn to a method. Rather, the claims are drawn to kits. Thereby, while the method claims have been amended to recite that the microorganisms are not cultured prior to hybridization, such a limitation does not apply to the claimed kits. The kits recite the open claim language of "comprising" and thereby allow for the presence of additional reagents.

Further, the dependent claims specifically require the inclusion of presumptive and enrichment media. Accordingly, there is no requirement for Versalovic, Amann (1990) or Amann (1995) to teach a method of in situ hybridization in which the microorganisms are not cultured prior to hybridization. Even if there was such a requirement, it is maintained for the reasons set forth in paragraph 5 above, that the combined references do suggest and provide a reasonable expectation of success of performing an in situ hybridization method for detecting macrolide antibiotic resistance without prior culturing of microorganisms.

7. Claims 91 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann (1995) and Amann (1990) the Stratagene catalog and further in view of Morotomi.

The teachings of Versalovic, Amann (1995 and 1990) and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed this rejection for the same reasons set forth in paragraphs 5 and 6 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

8. Claims 92, 93, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka (GenBank Accession No. U27270, June 1995) and Gingeras (US Patent No. 6228575).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference also teaches that an A to a G mutation at position 2059 confers resistance to clarithromycin in H. pylori. The reference teaches that the mutations can be detected by sequencing the nucleic acids of H. pylori and by restriction enzyme analysis. However, the reference does not teach detecting the mutations by performing hybridization and thereby does not teach probes to the 23S rRNA mutations.

It is noted that Versalovic (Figure 1) does teach the sequence of the wild-type 23S rRNA, as well s the sequence of the 2058 and 2059 mutations:

AGACGGAAAGACCCCGUGG – wildtype (clarithromycin sensitive)

AGACGG**G**AAGACCCCGUGG-- A2058G (clarithromycin resistant)

AGACGGA**G**AGACCCCGUGG – A2059G (clarithromycin resistant)

The A2058G sequence differs from the complement of SEQ ID NO: 1 only in that it is missing the 5' terminal nucleotide (i.e., the nucleotide complementary to the 3' terminal

T in SEQ ID NO: 1). Additionally, the complete sequence of the 23S rRNA of Helicobacter pylori was known at the time the invention was made and is specifically taught by Hiratsuka (GenBank Accession No. U27270).

Allele specific oligonucleotides for detecting and distinguishing between target nucleic acids which differ by one nucleotide were well known in the art at the time the invention was made. Additionally, alternative methods employing hybridization probes for the detection of single-nucleotide mismatches were also well known in the art. In particular, Gingeras teaches probes for detecting a target nucleic acid wherein the probes are able to distinguish wildtype and mutant nucleic acids that differ by one nucleotide and teaches hybridization methods for using such probes (see, for example, columns 13 and 14). Gingeras teaches including species specific probes in the probe sets. Additionally, Gingeras teaches labeling of hybridization probes (column 8) and the use of probe sets containing individual probes that are fully complementary to or which differ from the target nucleic acid by one nucleotide. The reference also exemplifies a number of allele specific probes which are of lengths from 15 to 20 nucleotides (see columns 24, 30 and 32). Gingeras (columns 20-21) teaches the use of the allele specific oligonucleotides to detect polymorphisms/mutations in rRNA regions that are associated with drug resistance.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have developed hybridization probes complementary to the "A2058G" sequence taught by Versalovic, wherein the probes comprised the sequence of SEQ ID NO: 1 or 10-30 mer fragments of SEQ ID NO: 1 because Gingeras

teaches how to make hybridization probes complementary to nucleotide sequences that contain a single-nucleotide mutation/polymorphism and teaches the use of such probes for the purposes of distinguishing between wildtype nucleic acids and nucleic acids which differ from wildtype nucleic acids by a single nucleotide. One of ordinary skill in the art would have been motivated to have generated such probes in order to have facilitated the detection of clarithromycin resistant strains of H. pylori and to have allowed for the simultaneous analysis of multiple samples and the detection of multiple mutations in H. pylori samples.

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed this by asserting that Gingeras teaches that a single probe cannot be used to discriminate between wildtype and mutant nucleic acids that differ by one nucleotide and that it is necessary to use probe sets to distinguish between species in order to classify an organism. This argument is not convincing because it does not relate to limitations recited in the claims. Firstly, the claims allow for the use of multiple probes. The specification (page 32) in fact states that it is essential to use 2 probes to detect H. pylori in situ. Secondly, the claims do not require classifying a microorganism. Rather, the claims require detecting macrolide antibiotic resistance. Therefore, teachings regarding the classification of microorganisms are not relevant with respect to the obviousness of the present claims. Lastly, Applicants have mischaracterized the teachings of Gingeras and the relevance of the teachings of Gingeras to the present rejection. Gingeras was cited for its teachings of how to develop an allele specific probe and of the optimum length for allele

specific probes. Also, Gingeras does teach that a single probe can be used to detect a target nucleic acid based on a single base pair mismatch when one has "additional knowledge about the target" – i.e., when a specific mutation has been identified in a target nucleic acid (see column 10).

Applicants assert that the cited references do not teach the specific oligonucleotide claimed in claim 92. It is asserted that the claimed probes are significantly shorter than the sequence disclosed by Hiratsuka. However, it is conflictive for applicant to argue on the one hand that they are enabling for all probes that can be used to detect any mutation associated with macrolide antibiotic resistance wherein the probe comprises any sequence, of any length from the peptidyltransferase region of any microorganims. And yet on the other hand, Applicants have asserted the criticality and unobviousness of a 10-30 mer probe comprising any 10 nucleotides of SEQ ID NO: 1. Applicants response should clarify this conflict in standards. Secondly, the A2058G probe of Versalovic differs from SEQ ID NO: 1 only in that it contains 1 additional 5' nucleotide. This is not considered to constitute a significant difference in length. The comment regarding the length of the sequence of Hiaratsuka is not relevant since Hiratsuka was not cited for its teaching of an allele specific probe. Rather, Hiaratsuka was cited for teaching the complete sequence of the 23S rRNA of Helicobacter pylori, which includes the A2058G probe of Versalovic and the 5' nucleotide missing from this probe.

9. Claims 86-90, 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka and Gingeras, as applied to claims 92-93 and 101-102 above, in view of the Stratagene Catalog.

The teachings of Versalovic, Hiratsuka and Gingeras are presented above. Additionally, Versalovic teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator. Versalovic teaches growing H. pylori in brain heart infusion agar containing fresh horse blood. It is a property of this media that it contains the reducing agent cysteine and a nitrogen source.

Accordingly, the combined teachings references teach a method for detecting H. pylori which requires the use of a 23S rRNA probe specific for the 2058 mutation of H. pylori, species specific probes, a presumptive medium, and an indicator substance for detecting antibiotic resistance. The combined references do not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of isolating H. pylori and

detecting H. pylori by hybridization in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect antibiotic resistant strains of H. pylori.

As stated in the MPEP 2111.03 which states "On the other hand, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone". In the present case, the recitation in the claims of a kit "for determining macrolide antibiotic resistance in microorganisms by in-situ hybridization," does not carry weight with respect to the obviousness of the kit and does not distinguish the claimed kit over the kits suggested by the prior art disclosures.

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed this rejection for the same reasons set forth in paragraphs 5 and 6 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

10. Claims 91 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka, Gingeras and the Stratagene Catalog, as applied to claims 86-90 and 94-97 above, and further in view of Morotomi.

The teachings of Versalovic, Hiratsuka, Gingeras and the Stratagene Catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

RESPONSE TO ARGUMENTS:

In the response of May 6, 2003, Applicants traversed this rejection for the same reasons set forth in paragraphs 5 and 6 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Carla Myers
July 20, 2004

CARLA J. MYERS
PRIMARY EXAMINER